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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,750	04/17/2001	James P. Elia	1000-10-C01	7239

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 11/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,750	ELIA, JAMES P.	
	Examin r	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-253* is/are pending in the application.

4a) Of the above claim(s) *6-203,206-235 and 240-242* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *204,205,236-239 and 243-253* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *6-253* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III in the response to requirement for restriction dated 25 August 2003 is acknowledged. The traversal is on the ground(s) that the instant fact situation should involve a genus/specie type of requirement for restriction and that the term "growth factor" is generic to genes, gene products and cells. Applicant also argues that the different types of growth factors all function in the same way to produce the same result. This is not found persuasive because each different type of growth factor requires its own search. A search for administration of protein growth factors would not reveal art relevant to gene or cell therapy for example. Thus, an undue search burden would be placed on the examiner to search and examine the claims as they read on all types of growth factors as defined by the Applicant. Also, administration of a protein acts via a mechanism that is distinct from administration of a gene or a cell. Administration of a protein involves the protein binding to a receptor and causing a cascade of biochemical responses from the cells bearing the receptors. Administration of a gene causes a transformation event, causing the cell to produce a protein that is not normally present or is present at a different time or quantity. Administration of a cell causes new cells to graft onto an existing tissue. Therefore, the different types of growth factors do not function in the same way to produce the same result.

The requirement is still deemed proper and is therefore made FINAL.

Claims 240-242 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement dated 25 August 2003.

Status of Application, Amendments, And/Or Claims

The following papers have been received from Applicant and are of record in the instant application:

1) transmittal form, specification, claims, drawings and declaration filed 4/17/01;

2) preliminary amendment and claims filed 4/17/01;

3) non publication request filed 5/29/01;

4) amendment and claims filed 9/3/03;

5) information disclosure statement filed 6/19/03;

6) 37 CFR 1.132 declarations of Drs. Lorincz and Heuser with attachments originally filed 6/23/03;

7) amendment and claims filed 7/1/03; and

8) response to restriction filed 10/6/03.

Claims 204, 205, 236-239 and 243-253 are under examination to the extent that they read on administration of cells, cellular products and derivatives of cells to a patient to form muscle to repair a dead or damaged portion of a heart.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A) New Matter

Claims 245, 248 and 249 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 245, 248 and 249 were added by amendment in a paper dated 17 June 2003. In this paper, Applicant did not specifically point to support for the new claim language in the disclosure as originally filed. Support for "multifactorial and non-specific" cells, intravenous injection of cells, intraluminal injection of cells and angioplasty delivery of cells could not be found by the examiner in the disclosure as originally filed.

B) Enablement

Claims 248 and 249 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of administering cells to a human patient via intravenous or intraluminal injection to form muscle and cause repair of a dead or damaged portion of the patient's heart. "Intravenous" is a term of art meaning administration into a vein. By definition, a vein is a blood vessel that leads toward the heart. "Intraluminal" is a term of art meaning administration into a "lumen" or cavity, such as the abdominal space or a blood vessel. It is noted that injection into the myocardium is an example of intramuscular administration, not intraluminal administration. Intraluminal administration into a heart is when a substance is injected directly inside a chamber of the heart. The specification provides no detailed definitions of "intravenous" or "intraluminal" and thus the common, art-accepted definitions provided above are used herein to interpret the claims.

The courts have determined several factors to be considered in making a determination of whether or not undue experimentation would have been required of the skilled artisan to make and use the claimed invention (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). These are:

1) quantity of experimentation required,

2) amount of direction/guidance presented in the specification,

3) presence or absence of working examples,

4) nature of the invention,

5) state of the prior art,

6) level of skill of those in the art,

7) predictability, and

8) breadth of the claims.

In the instant case, the quantity of experimentation required would be very large. The claims require administration of cells by intravenous or intraluminal injection to repair a dead or damaged portion of a heart. Administration of cells at a site distant to the site at which the cells are intended to adhere and grow had not been achieved in this art at the time of the invention. A great amount of experimentation would be required to determine how to administer the cells other than at the site of heart death/damage, cause the cells to travel to the site of heart death/damage, and then cause the cells to adhere such that repair of the dead/damaged heart portion could be achieved.

The amount of direction/guidance presented by the specification regarding these types of delivery is minimal. The words "intravenous" and "intraluminal" appear to be used only at p. 45 of the specification, and are restricted to the administration of VEGF proteins, not stem cells. The specification is silent with respect to overcoming the expected obstacles of targeting stem cells that are administered intravenously or intraluminally to the dead/damaged portion of the heart where they can adhere and exert their repairing effects. Thus, the skilled artisan is left with an invitation to experiment to determine how to administer cells intravenously or intraluminally as required by the claims.

There are no working examples directed to administering stem cells to dead or damaged portions of a heart. Although the specification contains prophetic statements

that stems cells can be administered to a dead or damaged portion of a heart to repair the heart, no actual experiments or data were disclosed.

The nature of the invention is extremely complex. Evidence of this can be found in the relevant art. As stated in Murry et al. (1996, J. Clin. Invest. 98:2512-2523), "the goal of limiting myocardial injury has been difficult to achieve clinically, because ischemic myocardium dies quite rapidly and most patients wait more than 3 h after coronary occlusion before seeking medical attention" (p. 2512, Introduction).

The state of the prior art indicates that only localized injection of cells can successfully treat damaged myocardium. See Murry et al. (*supra*), Klug et al. (1996, J. Clin. Invest. 98:216-224), Oakley et al. (2001, Ann. Thorac. Surg. 71:1724-1733), Chiu et al. (1995, Ann. Thorac. Surg. 60:12-8), Yoon et al. (1995, Tex. Heart Inst. J. 22:119-125), Koh et al. (1993, J. Clin. Invest. 92:1548-1554), Van Meter et al. (1995, J. Thorac. Cardiovasc. Surg. 110:1442-1448), and Koh et al. (1995, J. Clin. Invest. 95:114-121). All used intramuscular injection of cells directly into the myocardium.

The level of skill of those in the art is admittedly high.

The art is considered unpredictable, since it could not be predicted if cells administered intravenously or intraluminally would reach the site of heart death/damage. Also, the courts have acknowledged that inventions utilizing biological systems are unpredictable. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological

activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). In the instant case, not even one single embodiment has been exemplified for this unpredictable system.

The claims are considered broad, since no details of the administration method other than "intravenous" or "intraluminal" are recited. For example, no dosages or targeting molecules are recited. No specific types of cells that would be expected to travel to the desired site are recited.

Due to the large quantity of experimentation necessary to determine how to administer cells intravenously or intraluminally to achieve repair of a distant dead or damaged heart portion, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of targeting cells to a distant site, and the breadth of the claims, it is determined that undue experimentation would have been required of the skilled artisan to practice the claimed methods.

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 245 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. Claim 245 recites a cell that is "multifactorial and non-specific". It is not clear what is meant by these terms, as the terms are not used to describe cells in the art. For example, the term "multifactorial" is used to describe causes, effects and processes, not cells. The specification also provides no clear definition. Therefore, the metes and bounds of the claims cannot be determined.

Priority

The instant application is a continuation of 09/064,000, filed 21 April 1998. The instant disclosure appears to be virtually the same as that of '000, and thus benefit of the 21 April 1998 filing date is granted. The instant application is also a continuation-in-part of 08/837,608, filed 21 April 1997; 08/326,857, filed 21 October 1994; 08/087,185, filed 02 July 1993; and 08/053,886, filed 27 April 1993. None of these applications have support for the currently claimed invention, i.e., administration of cells to repair dead or damaged heart tissue. The '857, '185 and '886 applications are limited to disclosure of dental implants and clearly do not provide support for treatment of non-dental tissues such as heart. The word "heart" does not appear in any of those disclosures. The '608 application discusses hearts at p. 46, but this paragraph is limited to use of "genetic implants" to grow an "additional" heart. The '608 application does not suggest administering growth factors to repair a dead or damaged portion of a pre-existing heart.

Therefore, for the purposes of applying prior art, the effective filing date for the claimed invention is determined to be 21 April 1998.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 204 and 205 are rejected under 35 U.S.C. 102(b) as being anticipated by Murry et al. (1996, J. Clin. Invest. 98:2512-2523).

Murry et al. teach a method of growing a new portion of a pre-existing heart comprising placing stem cells in the body of the patient to grow muscle in the heart. See Results and Discussion sections, and Figure 1, showing new muscle growth in the heart.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 236-239, 243-247, 250, 251 and 253 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murry et al. (1996, J. Clin. Invest. 98:2512-2523).

Murry et al. teach a method of growing a new portion of a pre-existing heart comprising the steps of placing stem cells in the body of a patient and growing new muscle in said heart as well as forming an artery in said heart, thereby causing said

dead or damaged portion of said heart to be repaired. See Results and Discussion sections, and Fig. 1J showing muscle and capillaries. The recitation of "artery" in the claims is interpreted as any blood vessel leading away from the heart, including arterial capillaries, as such is recognized in the art and the specification does not provide an alternative definition for "artery" excluding capillaries. Note that the skeletal muscle satellite cells used by Murry et al. are characterized as stem cells, and thus are presumed to inherently possess the characteristics of being "mutlifactorial and non-specific" as recited in claim 245 (p. 2512, top of right paragraph). The cells were administered via intramuscular injection (p. 2513, middle of left column). The cells were suspended in a carrier (tissue culture media; p. 2513, middle of left column). All cells comprise genes, and thus the stem cells administered by Murry et al. also comprised a gene as recited in claim 253. Claim 253 does not require that the gene be heterologous with respect to the cell.

Murry et al. do not teach administration to a human patient. However, the rat system used by Murry et al. was clearly used as a model for human treatment (p. 2512, first paragraph of Introduction; p. 2520, second paragraph of Discussion section), and thus Murry et al. imply that the method can be applied to human patients.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of administering stem cells to repair a dead or damaged portion of a heart as taught by Murry et al. by treating humans as suggested by Murry et al. There was a reasonable expectation of success, since the rat system was clearly used as a model system for treating humans. The motivation to do

so would have been apparent to one of ordinary skill in the art, as it has always been highly desirable to repair dead or damaged heart tissue in human patients (see first paragraph of Introduction).

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claim 252 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murry et al. as applied to claims 236-239, 243-247, 250, 251 and 253 above, and further in view of Nabel et al. (U.S. Patent 5,328,470, issued 12 July 1994).

The disclosure of Murry et al. is summarized above.

Murry et al. do not suggest using an angioplasty balloon catheter to administer the cells. However, this was well known in the art at the time of the invention. For example, U.S. Patent 5,328,470 discloses the use of an angioplasty balloon catheter to administer cells to a selected site. See section IIA, columns 6-7.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Murry et al. by administering cells via an angioplasty balloon catheter as disclosed by Nabel et al. There was a reasonable expectation of success given Nabel et al.'s success in delivering cells via an angioplasty balloon catheter. The motivation to do so is also provided by Nabel et al. in that the angioplasty balloon catheter allows for precise placement of the cells in a damaged area including at the site of myocardial infarction (col. 17, li. 30-41).

Thus, the claimed invention as a whole was *prima facie* obvious over the art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (703) 308-2673. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne L. Eyler, Ph.D. can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER